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CRISPRs: molecular markers for tracking antibiotic resistant strains of Salmonella enterica

ABSTRACT

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Introduction to this issue

by Bonnie Marshall and Casi Kadangs (APUA staff)

Within the CDC's 2013 report on antibiotic resistance threats in the US, antibiotic-resistant, *Salmonella* is classified as a "serious" threat, meaning these bacteria present "a serious concern and require prompt and sustained action to ensure the problem does not grow."[1] In a landscape of historically evolving nomenclature, the speciation of *Salmonella* is complex and can be daunting. As members of the family *Enterobacteriaceae,* there are currently just two recognized species—*S. bongori* and *S. enterica* (with the latter having 6 main subspecies: *enterica*, *salamae*, *arizonae, diarizonae*, *houtenae*, and *indica*), but over 2,500 serovars, (serological variants) based on their reactions to specific antibodies. Of the two types of *Salmonella* serovars−typhoidal and nontyphoidal− the typhoidal serovars (*S.* Typhi and *S.*Paratyphi A, B and C) are confined to human hosts and cause typhoid and paratyphoid (enteric) fevers. These are spread from human to human—often shed by asymptomatic carriers who serve as important reservoirs –via direct contact, improperly handled food or via drinking water contaminated with sewage. Globally, an estimated 27.1 million people are infected with enteric fever, and mortality is high (12-30%) with 217,000 deaths annually.[2] In the developed world, most cases are brought back by travelers from endemic areas, which include the Indian subcontinent, the Caribbean, Africa, South and Central America, and South Asia, where antibiotic resistance levels are high. Where needed, treatment is often empirical—*before* the receipt of test results. Consequently, travel history is important and knowledge of local strains and resistance patterns is critical to effective therapy.

The more common salmonellae are the food-borne, non-typhoidal serovars, which are zoonotic in origin and frequently colonize asymptomatically the major livestock species: poultry, cattle and pigs. Other routes of infection include pets such as reptiles, turtles, lizards, snakes and more commonly, backyard chickens. In developed countries, the non-typhoidal salmonellae typically cause self-limiting gastrointestinal disease (food poisoning) with symptoms of diarrhea, fever, and abdominal cramps that run 5-7 days. In contrast, non-typhoidal salmonellosis in sub-Saharan Africa commonly presents as a much more serious and worrisome bloodstream infection (invasive non-typhoidal *Salmonella* or iNTS) with a case-fatality rate of 20-25% (2012).[3] The major serovars responsible for this form are Enteritidis and Typhimurium.

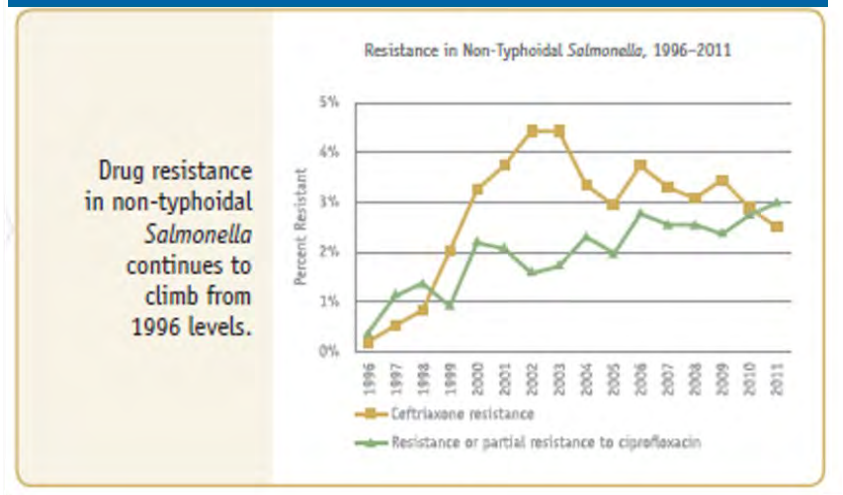
Salmonella has exhibited a remarkable ability to adapt, and changing trends in its emergence underscore the need for vigilant surveillance. As one type is controlled, another appears to fill the gap and new environments have become colonized, creating novel reservoirs of potential infection. In 2014 alone, there have been 9 *Salmonella* outbreaks in the U.S., with a current outbreak reported in 10 states linked to contaminated bean sprouts.[4] The emerging trends exhibited by *Salmonella* in this regard are described in more detail in this issue's feature article by Tauxe and colleagues.

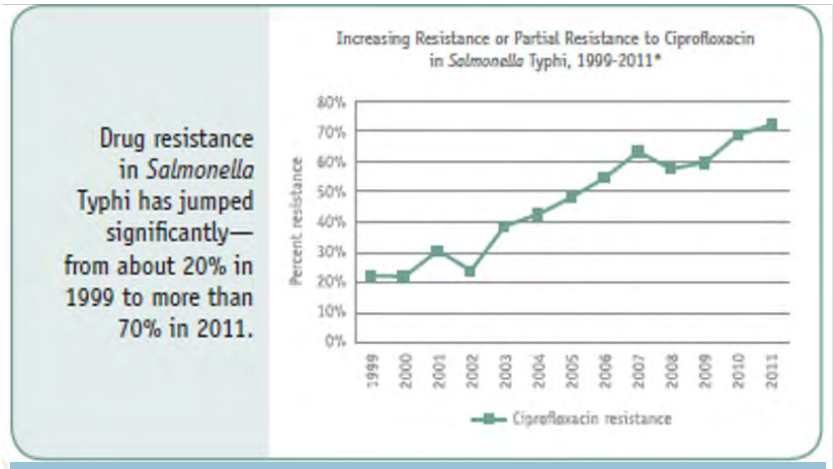
Table 1. Antimicrobial resistance in human *Salmonella* spp (non-typhoidal serovars) in 2012[1,2]

Antibiotic	Europe (EU/EEA)	Europe (other)	Africa	Asia	North & Central America	South America	Oceania
Current preferred agents							
Ciprofloxacin	5.4	19.5	20.5	22.7	10.5	9.5	15.4
Cefotaxime	1.1	0	2.1	1.5	0	4.8	0
Historical 1st & 2nd-line agents							
Ampicillin	27.8	4.9	20.2	24.3	3.4	9.5	15.4
Chloramphenicol	5.7	2.8	7.8	6.9	2.3	10.5	15.4
Sulfonamides	29.2	5.7	21.6	24.6	10.9	15.8	15.4
Trimethoprim	6.8	5	14.3	10.7	5.6	11.1	7.7
Gentamicin	4.8	7.5	7.1	4.6	2.8	4.8	7.7
Kanamycin	1.7	2.6	2.7	4	0.6	11.1	0
Streptomycin	23.9	5.3	10.7	10.9	5.1	14.3	7.7
Tetracyclines	30.2	11.4	26.2	25.7	11.5	10.5	15.4
Nalidixic acid	14.2	26.3	22.9	22.9	10.2	19	15.4
Multple agents							
MDR (≥ 3drugs)	28.9						
Ciprofloxacin & cefotaxime	0.2						

Source: adapted from EU Summary Report on Antimicrobial Resistance in Zoonotic and Indicator Bacteria from Humans, Animals and Food 2012. *EFSA Journal* 2014:12:3590
[1]Isolates outside of EU/EEA (dark blue) represent travel-associated cases
[2]Numbers of isolates tested: EU/EEA = >16,000; Europe (other) = ~40; Africa = ~750; Asia = ~1100; North & Central America = ~175; S. America = ~20; Oceania = 13

Figure 1. Increasing *Salmonella* resistance (1996-2011)





Source: CDC, www.cdc.gov/drugresistance/threat-report-2013/pdf/

Antibiotic resistance

While oral or intravenous rehydration therapy may be needed for fluid replacement in some cases, antibiotic therapy is contra-indicated for non-complicated salmonellosis, as antimicrobials can actually prolong the illness and excretion period in non-typhoidal strains. However, for serious infections, which tend to arise more frequently in infants, children, the elderly and the immunocompromised, antibiotics may be required. Resistance to the older first-line agents has eroded many inexpensive drug options and seriously compromised therapy in the developing world, leaving fewer, less accessible and more costly choices. In the U.S. alone, hospitalization for the 23,000 resistant *Salmonella* infections costs $365,000,000 annually.[1]

The acquisition of chloramphenicol resistance (S. Typhimurium ST313) some 75 years ago presented one of the earliest challenges to antibiotic therapy. Today, the high levels of resistance seen to ampicillin, streptomycin, sulfonamides, and tetracycline (the ASSuT phenotype) correspond to those antibiotics which have been commonly used in animals and formerly used commonly in humans (Table 1). As explained in this issue's feature articles by Tauxe and McDermott and colleagues, concern is currently focused on the rising trends in resistance to the newest antibiotics: ciprofloxacin and third-generation cephalosporins (Fig 1). Outside the US, azithromycin resistance is also being closely watched.[5]

Because resistance may vary between locales, surveillance and tracking of susceptibility patterns of this rapidly evolving, world-wide pathogen is considered important to management and control. To a certain extent, antimicrobial resistance in *Salmonella* appears to be serotype dependent, underscoring the importance of vigilant surveillance in this genus. *Salmonella* and other enteric pathogens in the U.S. are tracked by the National Antimicrobial Resistance Monitoring System, known as NARMS. To assist in tracking surveillance patterns in human isolates, the NARMS web site[6] features interactive graphics in which the latest available resistance data can be accessed for the major serovars. While, historically, such tracking has been largely dependent on culture-based serotyping methods, recent advances in molecular methodologies have revolutionized surveillance prospects by reducing costs, labor and time involved. In this issue, Dudley and coauthors discuss the design for improved molecular tools with particular emphasis on the use of CRISPRs (clustered regularly inter-spaced short palindromic repeats) that will enhance the subtyping of strains and tracking of outbreaks, as well as facilitate the study of evolution in this rapidly changing organism.

With a highly globalized food supply and increasing global travel, the worldwide spread of multi-drug resistant *Salmonella* has created considerable concern. As stated by Susan Grooters of the Center for Science in the Public Interest, "We have to act before it's too late. It's not *if* a multi-drug resistant outbreak that's too deadly to treat will occur, but *when*."[7]

Introduction continued on p. 15

Salmonella, the persistent pathogen

Robert Tauxe, M.D., M.P.H., **Felicita Medalla**, M.D., M.S., **Matthew Wise**, Ph.D., M.P.H, and **Jason Folster**, Ph.D., (Division of Foodborne, Waterborne and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia)

Salmonella has challenged us to develop new approaches for disease control since the dawn of modern public health. Concerns about *Salmonella enterica* serotype Typhi, for which the reservoir is human, brought microbiological methods to public health investigations late in the 1800's. More recently, since the 1980's, the global spread of serotype Enteritidis infections in chickens stimulated control efforts in egg-laying and broiler flocks around the world. Distinguishing strains using serotyping (part of public health surveillance since 1963), molecular markers, and antibiotic resistance has proved essential to trace the connections and pathways that lead to infection. Among these pathways, the appearance of multi-drug resistant* (MDR) foodborne *Salmonella* infections has raised concerns about the human health impact of antibiotics used in animal agriculture.[1]

In the United States, each year about 15 *Salmonella* infections per 100,000 people are diagnosed in clinical laboratories, or about 45,000 cases.[2] Because many ill people do not visit clinics or get cultured, the estimated annual number of actual infections is 1.2 million, of which one million are related to the domestic food supply.[3] Despite industry and regulatory efforts to make food safer, the incidence of reported *Salmonella* infections has not changed significantly since 1996, when active surveillance for foodborne infections began.[2] Over half of *Salmonella* infections are caused by the five most common serotypes (Typhimurium, Enteritidis, Newport, Heidelberg, and Javiana).[4(Appendix 1, Table 2)] Based on outbreak data from 1998-2008, the most common food sources for non-typhoidal salmonellosis were eggs (11.6–29.0% of infections), poultry (10.1–29.2%), and vine-stalk vegetables (9.6–22.9%).[4] (Appendix 1, Table 3)

Major outbreaks traced to food animal sources have stimulated development of enhanced regulations, such as the FDA egg safety regulation of 2010, and new poultry performance standards for parts and ground poultry now under active consideration by USDA.[5,6] Research into the pathways of contamination in these reservoirs has shown that some *Salmonella* can spend much time outside the intestinal tract. For example, three common serotypes, Enteritidis, Typhimurium, and Heidelberg, can colonize the reproductive tissues of the hen, and then spread vertically from the hen to the baby chick through the fertile egg. People consuming undercooked eggs from an infected chicken may get infected as well.[7,8] A recently identified source of *Salmonella* in ground beef may result from contaminated sub-cutaneous lymph nodes that wind up in the grind: biting flies can transfer *Salmonella* and other bacteria through the hide of the cow to lymph nodes.[9] Increasingly, major outbreaks have linked *Salmonella* to a growing variety of plant-derived foods, from peanut butter and hot peppers to sprouts and cantaloupes. These large outbreaks have stimulated development of new regulatory approaches through the Food Safety Modernization Act, focusing on fresh produce and processed foods.[10] They also led to important research exploring the ecology that connects enteric organisms and plants, revealing that some *Salmonella* carry genes with no identified role in infecting animals, that may help them adapt to life in plants.[11]

> *"Without a vaccine...or an accepted food treatment that makes all food safe, controlling* Salmonella *better depends in large part on understanding how contamination occurs and then blocking those pathways with changes in practices and policies around food."*

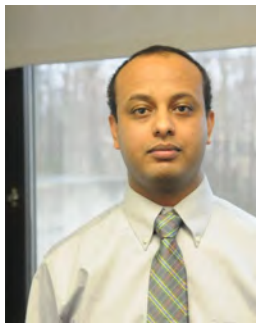
Outbreak investigations help to identify gaps in food safety and new opportunities for prevention. In 2013–14, an outbreak of 634 cases of *Salmonella* Heidelberg infections

* Defined as resistance to 3 or more classes of antimicrobial agents

Salmonella, *the persistent pathogen continued on p. 12*

Antibiotic resistance in *Salmonella*: data from the National Antimicrobial Resistance Monitoring System (NARMS)

Patrick McDermott, Ph.D, Direcor NARMS; Daniel Tadesse, DVM, Ph.D, Research Microbiologist, Div. of Animal and Food Microbiology (Office of Research, Center for Veterinary Medicine, U.S. FDA)

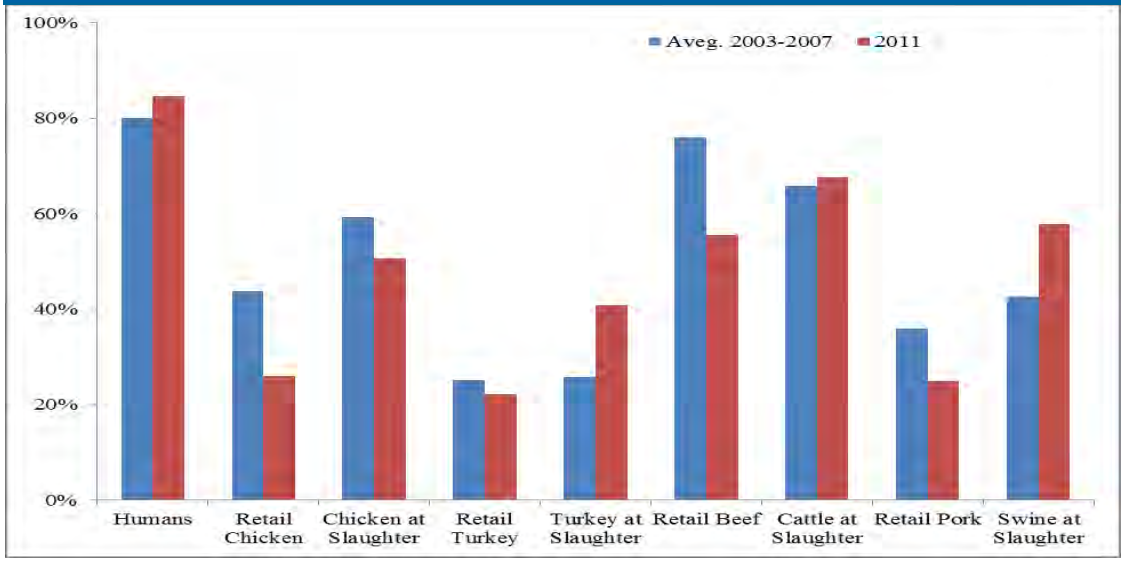


Non-typhoidal *Salmonella* causes approximately 1.2 million illnesses, 23,000 hospitalizations, and 450 deaths each year in the United States, wherein an estimated 100,000 infections and 40 deaths per year are caused by antibiotic-resistant strains.[1] Extended-spectrum cephalosporins and fluoroquinolones are the drugs of choice for treating patients with severe *Salmonella* infections. Azithromycin has more recently been recommended for diarrhea of unknown etiology.[2] Historically, ampicillin and trimethoprim-sulfa have been used to treat salmonellosis.

The latest NARMS *Salmonella* data extend through isolates analyzed from 2011.[3] In 2011, NARMS tested 2,344 human *Salmonella* isolates– 357 from retail meats, and 1,024 from healthy food animals at slaughter. *Salmonella* was isolated from 12% of ground turkey, 12% of retail chicken, 2% of pork chops and 1% of ground beef samples.

In 2011, NARMS found that 85% of *Salmonella* isolated from humans had no resistance to any of the antibiotics tested, the highest proportion since NARMS began, and up from an average of 80% from the 2003-2007 average baseline (Figure 1). This is a feature in the national trend data that is often overlooked, namely, that a given case of salmonellosis is more likely to involve a strain that is susceptible to all of the tested compounds compared to the previous 16 years. This may be due in part to the growing number of salmonellosis cases transmitted by foods other than animal byproducts. Among strains from retail meats and food producing animals, the data present a mixed picture, with increases in pansusceptibility in some sampling frames and decreases in others.

Figure 1. Pansusceptible *Salmonella* by source

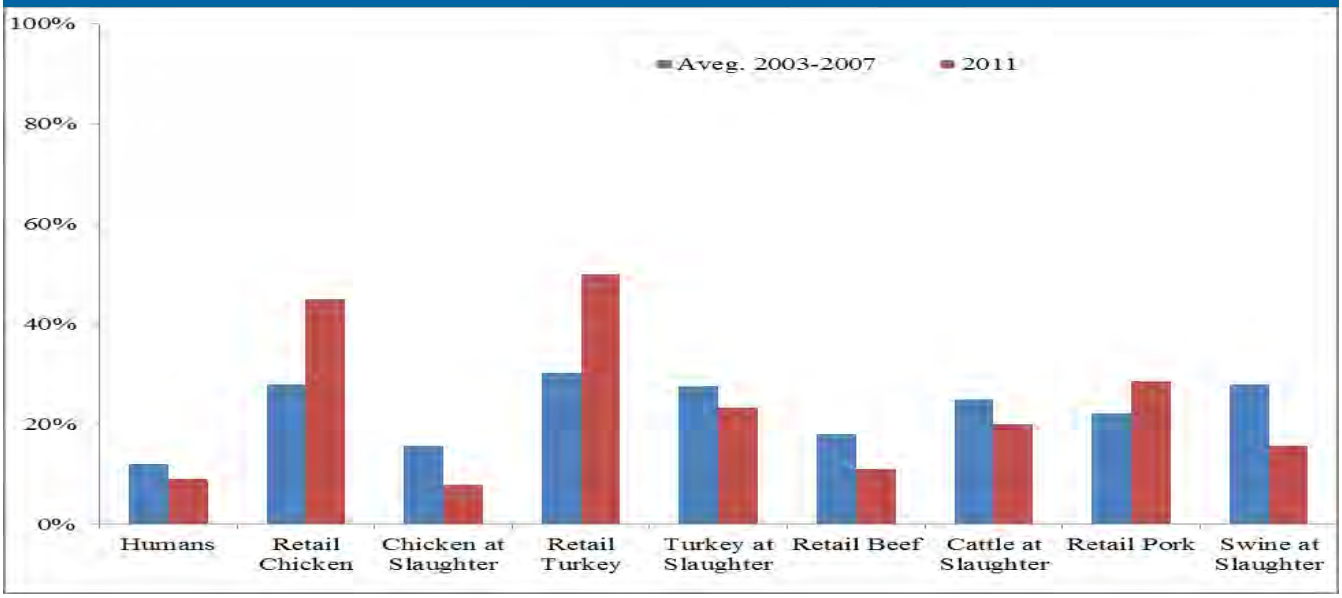


Resistance to First-Line Therapies

Fluoroquinolones are approved for control of certain respiratory infections in swine and cattle, but these agents are not approved for use in poultry (Animal Drugs @ FDA). During its 16-year history, NARMS has found ciprofloxacin^{R} *Salmonella* to be less than 0.5% among human isolates, less than 3% among retail meat isolates and less than 1% among animals at slaughter.

Ceftriaxone is a first-line therapy for severe *Salmonella* infections.[4] A closely related cephalosporin antibiotic, ceftiofur, is licensed for use in food animal production (Animal Drugs@FDA) and can induce cross-resistance. In contrast to cip^{R}, ceftiaxone resistance has increased in *Salmonella* isolates from all sources since testing began, especially in serotypes Newport, Heidelberg and Typhimurium in human strains.[5] These and other data led to FDA's April 2012 cephalosporin order which prohibits certain unapproved uses of cephalosporin drugs in cattle, swine, chickens and turkeys

Figure 2. Percent *Salmonella* resistant to three or more antibiotics



(http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm285704.htm).

Multidrug Resistance (MDR)

MDR in *Salmonella* from many sources has declined in the most recent year of data (Figure 2), although there is no evidence that drug use has declined. MDR strains among human (9%), chicken (8%), and swine (16%) isolates were at their lowest prevalence in 2011 since testing began. This is partly explained by the decreasing prevalence of serotype Typhimurium DT104 which was characteristically resistant to five agents.

How did we get here?

To better understand the historical evolution of resistance, we recently tested 2,117 banked historical isolates recovered from human clinical cases collected between 1948 and 1995 for susceptibility to the same agents used in NARMS. The data revealed significant increases in resistance to ampicillin (ranging between 1.6% in 1940s and 9.4% in 1990s), chloramphenicol (ranging between 0% in 1940s and 5.3% in 1990s), streptomycin (ranging between 3.2% in 1940s and 19.5% in 1990s), sulfamethoxazole (ranging between 1.6% in 1940s and 13.8% in 1990s) and tetracycline (ranging between 0% in 1940s and 19.5% in 1990s)

Figure 3. Evolution of antimicrobial resistance in human *Salmonella* from 1948-1995*

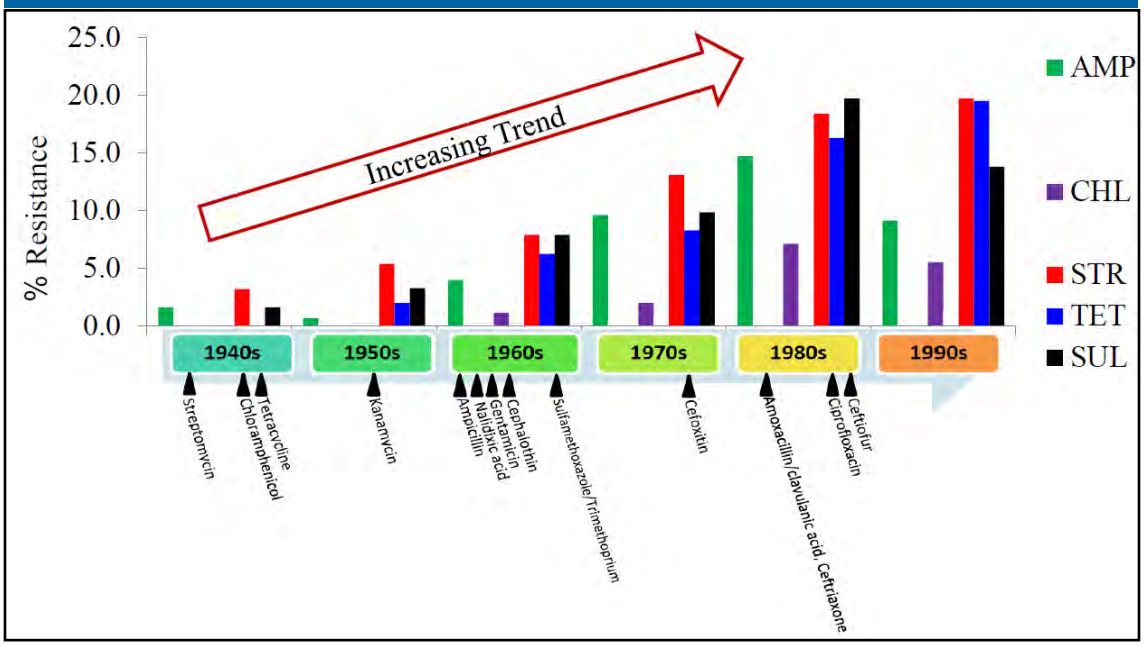
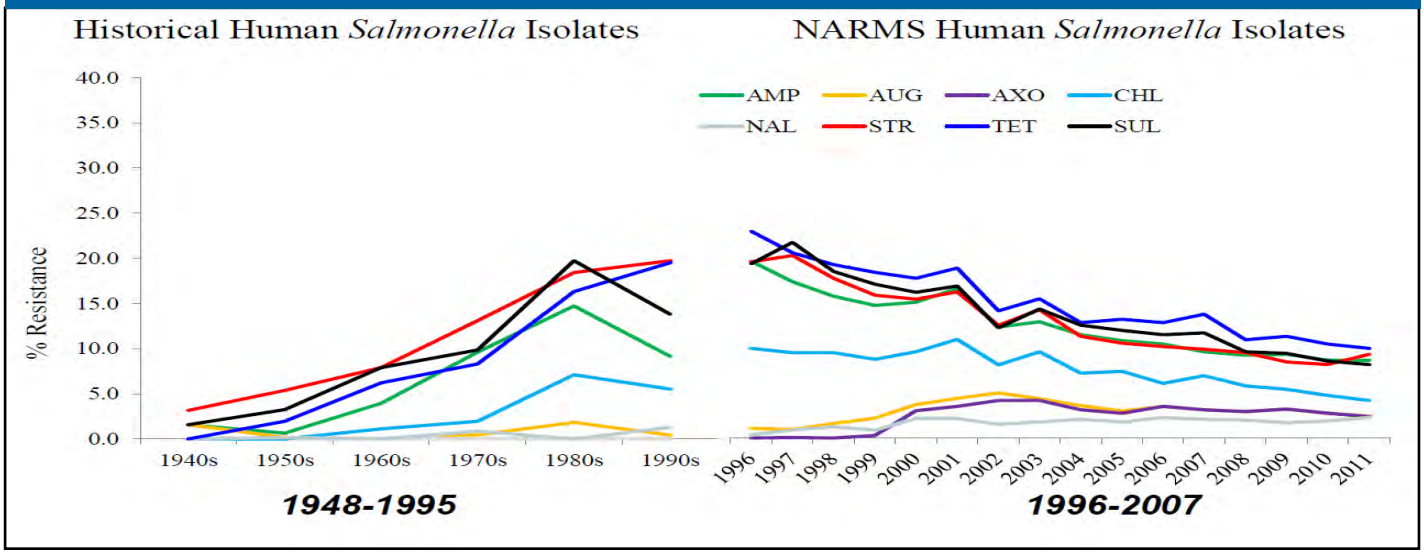


Figure 4. Antimicrobial resistance in *Salmonella*, past and present



during the study period (Figure 3, unpublished). This shows how resistance and the advent of antimicrobial classes are closely related temporally and don't always decline following exposure patterns. For example, chloramphenicol use in humans is very limited in the US, and not allowed in food producing animals. Despite this, resistance persists in *Salmonella*, as it does in other enteric organisms.[6] In our historical data set, more than 80% of strains with chloramphenicol resistance were also resistant to tetracycline, suggesting that chloramphenicol resistance persists in part by co-selection of linked determinants that encode for resistance to widely used antibiotics (e.g. sulfonamide and tetracyclines).

Historical data show that resistance to the older compounds increased steadily until the late 1990s, often linked together in MDR strains, and then began a steady decline (Figure 4).

What is the Bottom Line?

Because of the nature of antibiotic resistance and differences in resistance by serotype, it is not easy to speak of the overall resistance picture for *Salmonella.* In general, one can say that the most common resistances are for the older agents (sulfonamide, streptomycin, tetracycline, and ampicillin) and they are declining. We are most concerned with resistance to vital therapeutics like the fluoroquinolones where resistance remains low, and ceftriaxone where resistance has been rising, especially among certain serotypes. *For these two classes of drugs, extra-label uses are prohibited.* NARMS will continue to monitor the situation to measure the impact of these regulations and to identify emerging resistance hazards in the food supply.

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- NORM/NORM-VET 2013– Usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway

CRISPRs: molecular markers for tracking antibiotic resistant strains of *Salmonella enterica*

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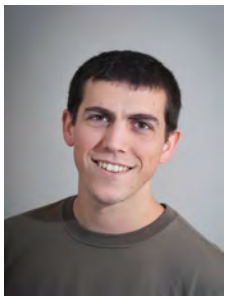
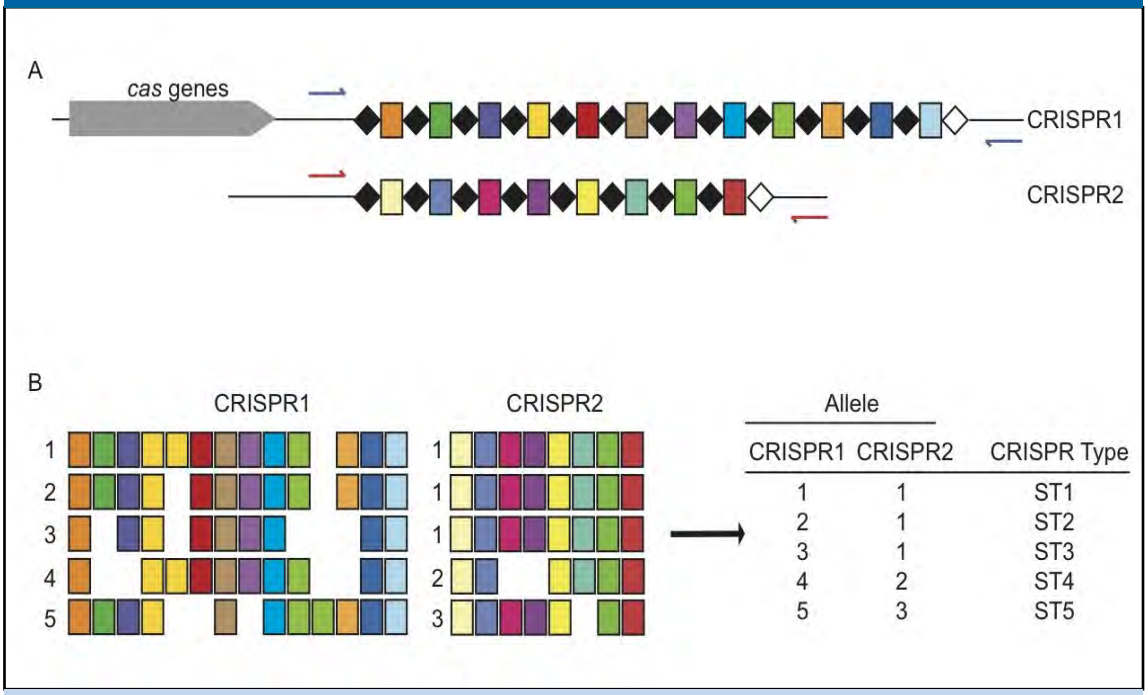


According to the U.S. Centers for Disease Control (CDC), non-typhoidal *Salmonella* are responsible for approximately one million cases of foodborne illness each year.[1] The serotype Typhimurium (ser. Typhimurium) is notable not only for its high number of human infections, but also for the prevalence of resistance to several different antibiotics. For example, ser. Typhimurium was the second most frequently observed serotype within laboratory-confirmed human infections in 2011,[2] and a 2012 report indicated that 50 of 295 isolates screened were resistant to a panel of traditional antibiotics including ampicillin, chloramphenicol, streptomycin, sulfisoxazole, and tetracycline. Also notable, 16 of the 295 isolates were resistant to ceftriaxone, which is commonly used to treat human infections.

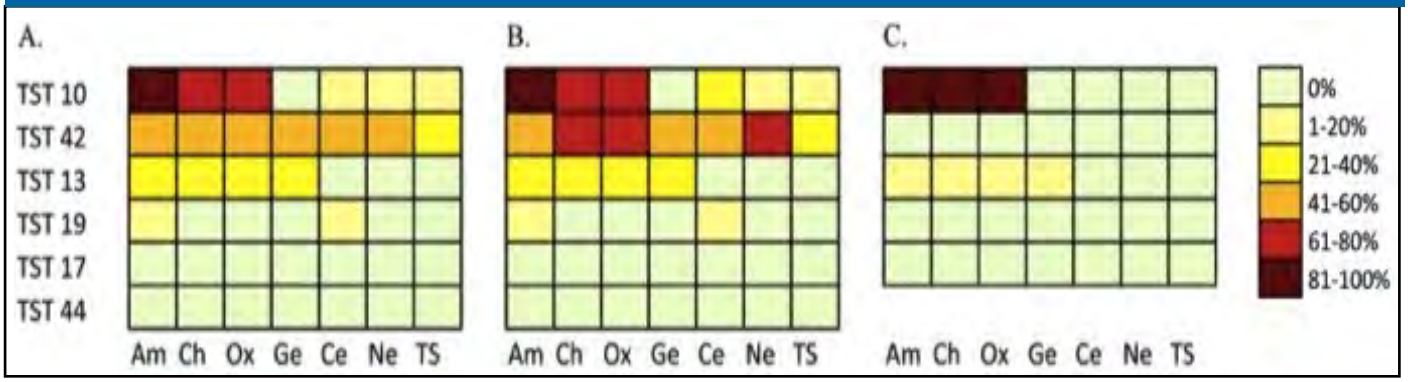
Figure 1. The architecture of a CRISPR-*cas* system, and basis of CRISPR-based typing



(A) There are two CRISPR loci in *Salmonella enterica* and eight *cas* genes (light gray arrow). The direct repeat sequences are shown as black diamonds, and the terminal repeat, which differs from the consensus sequence, is shown as a white diamond. Spacers are shown as colored rectangles, and unique spacers are represented by unique colors. Entire CRISPR spacer arrays are PCR amplified (the primers are indicated with red and blue arrows) and sequenced; (B) In the example shown, where there are two CRISPR arrays, a CRISPR type is defined by a combination of two unique alleles as shown in the table. A unique composition of spacers defines an allele, and the combination of CRISPR alleles is referred to as a sequence type (ST). Polymorphisms between strains occur from loss of some spacers and/or duplication of others; for example, the light green spacer in CRISPR1 is duplicated in allele 5. Figure is adapted from reference 5,

Foodborne outbreaks are often investigated using a combination of "traditional epidemiology" approaches such as surveying patients about recent foods consumed, plus "molecular epidemiology" DNA-based approaches that can distinguish between bacterial isolates at the strain level. Traditionally, public health laboratories and national laboratories such as the CDC have used pulsed field gel electrophoresis (PFGE) to identify strains, and to determine which food, patient, and environmental isolates are part of an outbreak. We and others[3-10] have

Figure 2: Heat map of resistance frequencies by sequence type



Animal Diagnostics Laboratory (ADL) isolates and human clinical isolates combined (A). ADL isolates only (B), and clinical isolates only (C). Antibiotics are represented by the following abbreviations: Am, ampicillin; Ce, ceftiofur; Ch, chlortetracycline; Ge, gentamicin,; Ne, neomycin; Ox, oxytetracycline; TS, trimethoprim-sulfamethoxazole. Figure is adapted from (13), Copyright © American Society for Microbiology

demonstrated that genetic structures called CRISPR, for Clustered Regularly Interspaced Short Palindromic Repeats, are also informative markers for *Salmonella* outbreak investigations. CRISPRs are genetic loci found in approximately half of all eubacteria, and are best known for their role in protecting cells against foreign DNA such as bacteriophage and plasmids.[11,12]

CRISPRs have two components: a set of Cas (CRISPR-associated) genes, and an array consisting of (in *Salmonella*) identical 29-base pair sequences (repeats) separated by unique 32 base pair sequences (spacers) (Fig. 1). New spacers may be acquired when bacteria are exposed to foreign DNA, resulting in diversification of CRISPR arrays between strains. We have demonstrated previously that PCR of CRISPR repeat-spacer arrays, followed by DNA sequencing, can complement PFGE data, assisting in the identification of which food and patient isolates are associated with an outbreak.[6]

We and others have also investigated whether DNA sequence data can be used to predict phenotypes such as antibiotic resistance and to follow the transmission of antibiotic resistant strains. In a previous study,[13] we sequenced CRISPR loci from a collection of ser. Typhimurium animal isolates obtained from farms in Pennsylvania between 2008 and 2011, and human isolates obtained from the Pennsylvania Department of Health over the same time period. Isolates that carried an identical complement of spacers were grouped into Typhimurium Sequence Types, or TSTs, and isolates from the six most common TSTs were screened for resistance to a panel of 18 antibiotics at Penn State's Animal Diagnostics Laboratory. We found that resistance to ampicillin, ceftiofur, chlortetracycline, gentamicin, neomycin, oxytetracycline, and trimethoprim-sulfamethoxazole was significantly associated with TST (Fig. 2). We also provided evidence that CRISPR sequence typing might identify subpopulations of ser. Typhimurium with distinct multidrug resistance patterns. For example, >60% of animal, and >80% of human TST10 isolates were characterized by a high frequency of resistance to ampicillin, chlortetracycline, and oxytetracycline. An overlap in TST and resistance patterns suggests that transmission of these strains is occurring between animals and humans. It was also notable that while resistance to these antibiotics was common among animal isolates of TST42, we did not observe any resistance among a small number of human isolates screened. We do not believe CRISPR itself plays a role in antibiotic resistance, but this study suggests that CRISPR may be appropriate targets for tracking the transmission of antibiotic-resistant strains of bacteria from their reservoir to the human population. The approach taken here may apply to other pathogenic organisms as well; indeed a correlation between CRISPR and antibiotic resistance has also been noted for *Enterococcus faecalis*[14] and the plant pathogen *Erwinia amylovora*[15]

DNA sequence-based methodologies are increasingly used during epidemiologic investigations due to the rapidly decreasing cost, the ease of data analysis, and the ability to generate data in a high-throughput, automated manner. Sequencing and analysis of targeted DNA regions is being replaced by full genome analysis.[16] These tools will undoubtedly increase the accuracy of predictions by revealing all known antibiotic resistance genes carried by an isolate, and should provide a fine level of resolution needed to predict levels of resistance. Such goals are being pursued by many groups,

including the Food and Drug Administration's Whole Genome Sequencing Program,[17] and represent an exciting tool for providing health care workers with information needed for the appropriate selection of antibiotics during treatment.

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Salmonella, *the persistent pathogen continued from p. 5*

was linked to chicken from one poultry company; many infections were due to MDR strains.[12] The variety of chicken products consumed by ill persons was traced back to three different processing establishments in California owned and operated by a single poultry company. The USDA's Food Safety and Inspection Service identified outbreak strains of *Salmonella* in all three facilities, raising questions about where in the breeding pyramid the outbreak strains might have been introduced. Could transovarial transmission of *Salmonella* from hens to chicks lead to *Salmonella* in chickens destined for human consumption, as it does with eggs? And therefore, could the use of antibiotics in preceding generations of birds be relevant to public health?

Antibiotic resistance in *Salmonella* is an important issue for clinical and public health. Most infections resolve without treatment, but when treatment is needed, resistant infections may not respond to first-line drugs and are associated with longer illness and more severe outcomes. Resistant *Salmonella*, like *C. difficile*, can complicate treatment of other infections.[13,14] Antibiotic resistance in *Salmonella* in the United States is tracked in the collaborative National Antimicrobial Resistance Monitoring System (NARMS). In NARMS, CDC tracks resistance in strains infecting humans by testing 1 in 20 isolates submitted to public health laboratories, FDA tracks resistant isolates from retail meat and poultry and the USDA tracks resistant isolates in food animals at slaughter. As of 2012, this report card on resistance shows some progress for *Salmonella*, and some areas of concern.[15] While *Salmonella* infections have not decreased, the frequency of MDR has declined, driven mainly by a decline in MDR strains of serotypes Typhimurium and Newport that emerged in the 1980s and the 1990s. Full resistance to ciprofloxacin has remained low in non-typhoidal *Salmonella* serotypes; however, decreased susceptibility to ciprofloxacin is notable, particularly in serotype Enteritidis. These strains are also typically resistant to first-generation quinolones, e.g., nalidixic acid. In the U.S., nalidixic acid resistance in serotype Enteritidis has risen from 0.9% in 1996 to 7.7% in 2012 and now accounts for 50% of nalidixic acid resistance observed among *Salmonella*.[15] However, nalidixic acid resistance among serotype Enteritidis from slaughtered food animals and retail meat in the U.S. remains extremely rare. Persons with nalidixic acid-resistant serotype Enteritidis infections in the U.S. have often acquired it during international travel.[16]

"The current administration's budget for 2015 includes support to start testing all human Salmonella *isolates for resistance."*

Resistance to the third-generation cephalosporin, ceftriaxone, is an important concern as this is the drug of choice for treating invasive pediatric infections. Although overall resistance to ceftriaxone has remained low in *Salmonella*, resistance to ceftriaxone has increased in serotype Heidelberg and some less common serotypes. Outbreaks of MDR serotype Heidelberg infections have been linked to consumption and handling of poultry. Use of a third-generation cephalosporin in poultry may contribute to resistance to ceftriaxone in human serotype Heidelberg infections.[17]

In the U.S., ceftriaxone resistance in *Salmonella* is usually due to the production of a CMY beta-lactamase, and the gene encoding this enzyme, blaCMY, is commonly carried by plasmids.[18,19] The appearance of this gene, located on an MDR-IncA/C plasmid, suddenly made *Salmonella* Newport resistant to ceftriaxone in the 1990s. Though that strain is now almost gone, the blaCMY gene, now repackaged in an IncI1 plasmid, has spread to numerous *Salmonella* serotypes and is responsible for the high degree of ceftriaxone resistance seen among serotype Heidelberg from humans and food animals.[20,21] IncI1 plasmids encoding blaCMY have been shown to be responsible for ceftriaxone resistance in several recent outbreaks of salmonellosis (CDC unpublished data).

In developing parts of the world, typhoid fever, due to *Salmonella* Typhi, is an important cause of illness and death. Most serotype Typhi infections in the United States are acquired during international travel; most travel-related infections are resistant to antibiotics. Among serotype Typhi strains, 70% are resistant to a quinolone antibiotic, raising concerns that ciprofloxacin may not be as effective for treatment.[15]

Severe infections with non-typhoidal *Salmonella* serotypes are also of great concern in other parts of the world. MDR strains of serotype Typhimurium have emerged in sub-Saharan Africa, where invasive infections are a particular problem in infants, young children, and young adults with HIV infection. A strain of serotype Kentucky that appeared first in North Africa and the Middle East, and then became resistant to ciprofloxacin and other agents, has spread to turkey production in Europe causing human illness there.[22,23]

Salmonella continues to challenge clinicians, public health scientists, and food safety officials. The Healthy People 2020 goals include reducing the incidence of non-typhoidal

Salmonella infections by 25%, as well as preventing an increase in resistance to important antibiotics.[24] Without a vaccine that renders the population immune, or an accepted food treatment that makes all food safe, controlling *Salmonella* better depends in large part on understanding how contamination occurs and then blocking those pathways with changes in practices and policies around food. Detecting and investigating outbreaks, critical to defining those pathways, depends on modern public health surveillance. For decades, microbiological subtyping has proved of great worth in enhancing public health surveillance. Now, as new rapid diagnostic test platforms help diagnose these infections at the point of care so that empiric treatment can begin quickly, laboratories still need to isolate and characterize the pathogen infecting the patient to guide treatment and drive public health surveillance. At the same time, surveillance can become more powerful as whole genome sequence (WGS)-based subtyping of those isolates becomes standard in the public health system. Surveillance for antimicrobial resistance can also be improved. The current administration's budget for 2015 includes support to start testing all human *Salmonella* isolates for resistance. Coupled with the growing use of WGS-based methods, public health investigators, agricultural scientists, and regulatory authorities will soon have far more powerful tools to understand how *Salmonella* spreads from reservoirs to people, how and where resistance genes transfer from one strain to another, and how to interrupt spread more effectively.

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Salmonella in the News

Large *Salmonella* outbreak marked by MDR and high morbidity

According to the CDC, a *Salmonella* Heidelberg outbreak linked to tainted chickens from Foster Farms in California resulted in the hospitalization of 38% of its 634 victims. The outbreak, which extended from Mar 2013 to Aug 2014 and covered 29 states, is now ended, and while there were no deaths, this is higher than the average hospitalization rate. Tested strains have been found to be resistant to multiple antibiotics including tetracyclines, penicillin, sulfas and aminoglycosides. These antibiotics are commonly used in animals raised for food. FDA data show that approximately 15% of turkey and chicken in U.S. stores are contaminated by *Salmonella*, which exhibits resistance about 75% of the time. Current FDA guidelines for antibiotic use in animal husbandry are under criticism for being insufficiently stringent and for allowing too much overlap between their use for therapeutic and nontherapeutic purposes.

Latest *Salmonella* outbreak traced to bean sprouts

An ongoing *Salmonella* Enteritidis outbreak in the Northeast U.S. has been traced to bean sprouts from a company in Brooklyn, New York. The outbreak is reported to have affected over 87 people in about 11 states with 24 hospitalizations. To date, no antibiotic resistance has been reported. FDA data show 30 outbreaks linked to sprouts since the 1990s, leading some to believe that sprouts are a risky food.

EU releases report on antimicrobial resistance for 2012

In March, 2014 The European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC) released a report titled, *The European Union Summary Report on Antimicrobial Resistance in Zoonotic and Indicator Bacteria from Humans, Animals and Food in 2012*. The comprehensive report, which compiled data from 26 European Union member states, found that human *Salmonella* isolates showed high frequencies of resistance to ampicillin, sulfonamides, and tetracyclines. Resistance to third-generation cephalosporins and fluoroquinolones remained low. Resistance was also detected in *Salmonella* isolates from fowl, pigs and cattle, and high to very high resistance to fluoroquinolones was found in turkeys, fowl and broiler meat isolates.

Salmonella shedding increases in animals fed antibiotics

Scientists at Stanford University School of Medicine have found that a majority of mice infected with *Salmonella* Typhimurium and given streptomycin shed more bacteria and became sicker than they were prior to receiving the antibiotic. In contrast, a small percentage of mice who normally shed high amounts of *Salmonella* in their feces (i.e., "super-spreaders") remained asymptomatic and were unaffected by either the disease or by the antibiotic treatment. Because the immune systems of super-spreaders and non-super-spreaders are in differing states, it may be possible to devise a blood test to quickly identify super-spreaders.

These observations have led the researchers to believe that this same phenomenon can occur in livestock that are routinely fed antibiotics. If verified, the findings have implications for the growing global concern of antibiotic resistance, since antibiotic-fed livestock are viewed as an important contributor to the problem.

CDC resistance stats highlight need for improvement in beef industry

Over the last two decades, the beef industry in the U.S. has made significant strides in reducing the number of disease outbreaks related to beef. However, at the October 2014 Beef Safety Conference organized by the North American Meat Association, the CDC reported that, despite these improvements in the industry, beef is still the third most common food associated with illness. Between 2009 and 2013, there were 75 outbreaks linked to beef, with 23% of those caused by *Salmonella.* The CDC has tracked about 95 outbreaks due to *Salmonella*-tainted beef since the 1970s and has antimicrobial resistance data for 14 of those outbreaks. 57% percent of isolates bore resistance to at least one class of antimicrobial agents and resistant strains were found to be more virulent – causing more hospitalizations than non-resistant strains (23% vs. 9%). One of the main recommendations in avoiding future beef-related outbreaks is more judicious use of antibiotics in the animal husbandry.

USDA petitioned to reclassify *Salmonella* as "adulterants"

On October 1, 2014, The Center for Science in the Public Interest (CSPI) petitioned the U.S. Department of Agriculture (USDA) to classify four antibiotic-resistant strains of *Salmonella* as "adulterants" in food under federal law. These strains, found in meat and poultry, are linked to over 2,000 illnesses, 424 hospitalizations, and 8 deaths, which qualifies them for consideration as adulterants. CSPI has criticized the government agency for being inconsistent and arbitrary in its handling of recalls, even as thousands of consumers have suffered in multiple *Salmonella* outbreaks in 2014 alone. CSPI filed a similar petition in 2011 that was denied by the USDA, which believes that proper cooking by consumers is sufficient to kill *Salmonella*. In light of the recent outbreaks, however, CSPI counters that proper food handling by consumers is inadequate, and that more stringent measures are needed in order to minimize future outbreaks. If passed, the bill would broaden the agency's definition of "adulterated" to include emerging pathogens "associated with actual or potential human illnesses or death, including at minimum, pathogens such as antibiotic-resistant strains of *Salmonella* or enterohemorrhagic (EHEC) and Shiga toxin-producing serotypes of *E. coli*." It would allow rapid removal of tainted foods from the marketplace before they could cause illness.

Consumer Reports finds loopholes in ground turkey processing

In 2013, Consumer Reports carried out an investigation of ground turkey with findings that caused considerable concern. 257 samples were tested for *Enterococcus*, *E.coli*, *Salmonella*, *Staphylococcus aureus*, and *Campylobacter*, and about 90% of the samples contained at least one of the five target bacteria tested. Nearly all of the isolates proved to be resistant to one or more antibiotics. Significantly, the samples labeled "organic" or "raised without antibiotics" were just as likely to harbor these bacteria, although the likelihood of being antibiotic-resistant was less. A plausible reason for this widespread bacterial contamination could be due to lax federal regulations in meat processing. The Food Safety and Inspection Service (FSIS) allows half of the ground turkey samples it tests to be tainted by *Salmonella*. In actuality, the USDA ought not to allow more than 12% contamination in ground turkey samples. At this level, proper handling and cooking by consumers is sufficient to kill the bacteria present in the meat.

Recommended Resources

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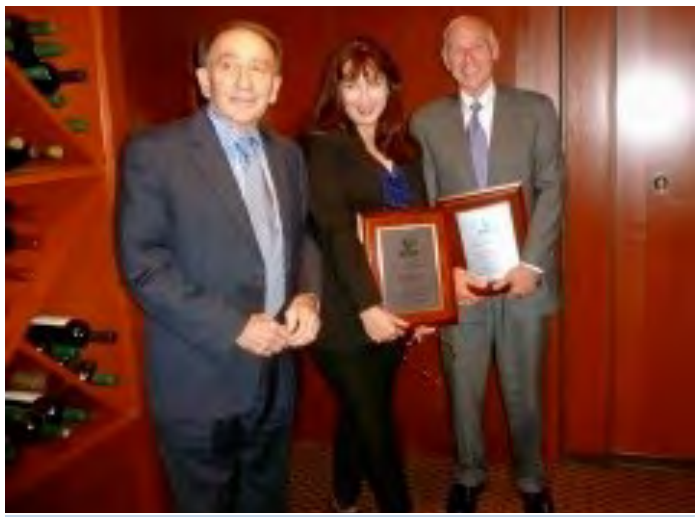
APUA News and Chapter Updates

APUA bestows Leadership Awards

In November, APUA held a dinner award ceremony in honor of the 2014 Leadership Award Recipients - Maryn McKenna and John LaMattina. Maryn McKenna was recognized for her journalistic efforts in bringing antibiotic resistance to the forefront of public consciousness. McKenna is a Senior Fellow at the Schuster Institute for Investigative Journalism at Brandeis University, writes for several publications including Wired and National Geographic, and is the author of *SUPERBUG: The Fatal Menace of MRSA*. John LaMattina was honored for his decades of advocacy for better antibiotic stewardship. LaMattina writes a column in Forbes on pharmaceutical and life science issues, and authored the book- *Devalued and Distrusted.*

APUA President, Dr. Levy, provided introductions and remarks and presented the award plaques. The event was attended by members of APUA's Board, as well as APUA staff, corporate sponsor representatives, and other APUA friends and well-wishers.



From left: APUA President, Stuart Levy, with APUA Leadership Awardees Maryn McKenna and John LaMattina

Brandeis hosts screening of *Resistance* documentary

On November 13th, 2014 Brandeis University hosted a viewing of the film *Resistance*. It was followed by an interactive audience discussion with a panel of experts, which included APUA vice-president Tom O'Brien, 2014 Leadership Award recipient, Maryn McKenna, and *Resistance* filmmaker Michael Graziano.

Resistance uses interviews, archival material, and vérité footage to untangle the web of factors behind the global crisis of antibiotic resistance. Experts and ordinary individuals who have faced this crisis first-hand reveal how our use of antibiotics has created profound challenges, not only for hospitals, but for much of modern life – from food, to governance, to personal health. With their insights, the film clarifies what's at stake, what's driving the problem and how we might turn the tide.

CRP attracting interest as point-of-care test

C-reactive protein (CRP) is available as a point-of-care test in parts of Europe where it is used as a diagnostic tool in differentiating the need for antibiotic therapy in cases of lower respiratory tract infection. In May 2014, APUA convened a summit of U.S. and international experts who reviewed the available literature and discussed the pros and cons of implementing CRP as a rapid point-of-care-diagnostic by U.S. primary care physicians. As an outcome of that meeting, a manuscript titled "When to give Antibiotics for Respiratory Tract Infections among Outpatients: Are the Europeans on to a Better Way?" authored by co-moderators Drs. Robert Gaynes and Stuart B. Levy, has been submitted for publication and is presently under review. In the interim, the British National Institute for Health and Care Excellence (NICE) has issued new guidelines in which CRP testing has been introduced as an integral part of its strategy for diagnosing pneumonia. The guidelines recommend considering a point-of-care CRP test in cases where a pneumonia diagnosis has not been made following clinical assessment and it is not clear whether antibiotics should be prescribed. Additionally, in a new prospective observational study by Nijman et. al., the authors have provided new evidence supporting the value of both CRP and procalcitonin testing for detecting serious bacterial infections in febrile children in the emergency care setting.

APUA participates in CDC's *Get Smart Week* 2014

APUA staff participated in a CDC Twitter chat, which was a part of its *Get Smart Week* 2014 activities. The Twitter chat featured CDC experts Drs. Tom Chiller, Lauri Hicks, and Loria Pollack who shared current data and trends in the field of antibiotic resistance. They also answered questions that were fielded by participants of the chat.

Get Smart Week is an annual event hosted by the CDC to raise awareness and educate the public on the serious issue of antibiotic resistance. Several events are organized to support this central theme, and supporters are encouraged to take part in creative ways. The Twitter chat is one of the activities that is used to generate conversation on a large scale.

APUA President Levy to speak at global health conference

On March 26, 2015, Dr. Stuart Levy will join speakers Ramanan Laxminaryan, Maryn McKenna, Lance Price and Kevin Outterson in a Boston, MA CUGH Global Health Conference titled "Mobilizing Research for Global Health. The group will speak in a session focused on the challenge of declining antibiotic effectiveness.

Maryn McKenna was the recipient of APUA's 2014 Leadership Award.

From L-R: Prof. Roman S. Kozlov, Director of the Institute of Antimicrobial Chemotherapy (IAC) of Smolenk State Medical Academy, and President of IACMAC; Andrei Kuzmin, head of Health Department, Vladivostok, Russia; Pavel Serebryakov, Promorsky Krai vice-governor on Public Health, Vladivostok, Russia

Tribute

University of Illinois remembers Dr. Abigail Salyers

Abigail Salyers, a long-time member of the APUA Scientific Advisory Board, was remembered by the Illinois Department of Microbiology in a memorial symposium held Saturday Nov 8, 2014 in Urbana Illinois: *Microbial Diverstiy—a tribute to the life and work of Abigail Salyers*. The day-long seminar featured talks by long-time colleagues on microbial diversity in the environment, microbial response to the environment and gene regulation, and microbial mechanisms of disease, followed by personal scientific tributes by Drs. Whitaker, Fouke and Wilson of the University. More information on Dr. Salyers, and the Abigail A. Salyers Graduate Student Fellowship Award in Microbiology, established in her honor, can be accessed here.

APUA-Russia

APUA-Russia was established in 1997 in affiliation with the Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC). IACMAC members (over 1,500 in Russia) frequently participate in national and international conferences and symposiums organized jointly by IACMAC with APUA.

IACMAC activities include several annual meetings (one international congress in Moscow and two international conferences in different parts of Russia), antibiotic resistance monitoring, educational workshops and meetings with online and offline schooling of bacteriologists, clinicians and clinical pharmacologists and publishing activities (e.g. the official international-peer-review quarterly publication "Clinical Microbiology and Antimicrobial Chemotherapy", practical guidelines on anti-infective chemotherapy, etc.).

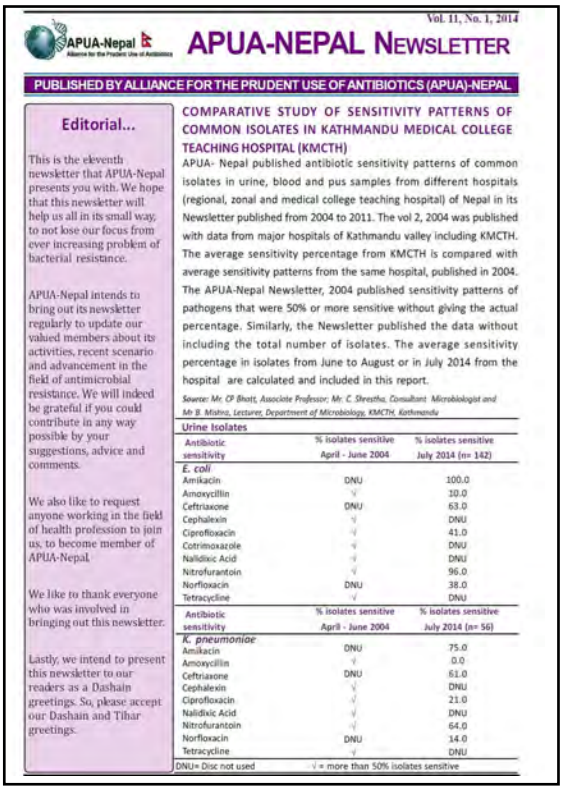
Three annual meetings occurred in 2014: IV Siberian conference in Krasnoyarsk on 3-4 April; XVI International Congress in Moscow on 21-23 May (reported in Issue #2) and the 2014 V Far-East Conference on Antimicrobial Chemotherapy in Vladivostok on October 16-17. Attendees included 1036 specialists from 19 regions of Russia and other countries, including Belarus, China, Great Britain, Italy, Sweden and Ukraine, as well as clinical pharmacologists, bacteriologists, microbiologists, therapeutists, and other clinical specialists. For 2015 meetings, see Upcoming Events.

APUA-Nepal

APUA-Nepal published its 11th Newsletter in December, a publication produced consistently since its inception. Several accomplishments and chapter activities were highlighted including:

- The publication and distribution of the Vol. 10 issue to various medical colleges and hospitals across the country
- New Antibiotic Treatment Guidelines, drafted by APUA-Nepal, have been approved by the Nepali Ministry of Health and Population (MoHP) following several rounds of verification and discussion by experts and stakeholders. A January 2015 meeting by the MOHP will plan dissemination of the new guidelines.
- The APUA-Nepal president was interviewed by BBC Nepal in October 2014 on the state of antibiotic use in the country and the recently approved Antibiotic Treatment Guidelines.
- The Eighth General Body Meeting was held in November, re-electing the existing executive committee and filling one vacancy.

The complete Newsletter can be found here.



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APUA-NEPAL NEWSLETTER

PUBLISHED BY ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS (APUA)-NEPAL

Editorial...

This is the eleventh newsletter that APUA-Nepal presents you with. We hope that this newsletter will help us all in its small way, to not lose our focus from ever increasing problem of bacterial resistance.

APUA-Nepal intends to bring out its newsletter regularly to update our valued members about its activities, recent scenario and advancement in the field of antimicrobial resistance. We will indeed be grateful if you could contribute in any way possible by your suggestions, advice and comments.

We also like to request anyone working in the field of health profession to join us, to become member of APUA-Nepal.

We like to thank everyone who was involved in bringing out this newsletter.

Lastly, we intend to present this newsletter to our readers as a Dashain greetings. So, please accept our Dashain and Tihar greetings.

COMPARATIVE STUDY OF SENSITIVITY PATTERNS OF COMMON ISOLATES IN KATHMANDU MEDICAL COLLEGE TEACHING HOSPITAL (KMCTH)

APUA- Nepal published antibiotic sensitivity patterns of common isolates in urine, blood and pus samples from different hospitals (regional, zonal and medical college teaching hospital) of Nepal in its Newsletter published from 2004 to 2011. The vol 2, 2004 was published with data from major hospitals of Kathmandu valley including KMCTH. The average sensitivity percentage from KMCTH is compared with average sensitivity patterns from the same hospital, published in 2004. The APUA-Nepal Newsletter, 2004 published sensitivity patterns of pathogens that were 50% or more sensitive without giving the actual percentage. Similarly, the Newsletter published the data without including the total number of isolates. The average sensitivity percentage in isolates from June to August or in July 2014 from the hospital are calculated and included in this report.

Source: Mr. CP Bhatt, Associate Professor; Mr. C. Shrestha, Consultant Microbiologist and Mr B. Mishra, Lecturer, Department of Microbiology, KMCTH, Kathmandu

Urine Isolates

Antibiotic sensitivity	% isolates sensitive April - June 2004	% isolates sensitive July 2014 (n= 142)
E. coli		
Amikacin	DNU	100.0
Amoxycillin	√	30.0
Ceftriaxone	DNU	63.0
Cephalexin	√	DNU
Ciprofloxacin	√	41.0
Cotrimoxazole	√	DNU
Nalidixic Acid	√	DNU
Nitrofurantoin	√	96.0
Norfloxacin	DNU	38.0
Tetracycline	√	DNU
Antibiotic sensitivity	**% isolates sensitive April - June 2004**	**% isolates sensitive July 2014 (n= 56)**
K. pneumoniae		
Amikacin	DNU	75.0
Amoxycillin	√	0.0
Ceftriaxone	DNU	61.0
Cephalexin	√	DNU
Ciprofloxacin	√	21.0
Nalidixic Acid	√	DNU
Nitrofurantoin	√	64.0
Norfloxacin	DNU	14.0
Tetracycline	√	DNU

DNU= Disc not used √ = more than 50% isolates sensitive

Upcoming Events

February 5, 2015: The British Society for Antimicrobial Chemotherapy (BSAC) Roundtable on Re-stoking the Therapy Pipeline– how to stimulate the development of new antibiotics, diagnostics and novel therapies London, England

February 26-28, 2015: Australian Society for Antimicrobials (ASA) 16th Annual Meeting, Brisbane, Queensland, Australia

March 18-21, 2015: Australasian Society for Infectious Diseases (ASID) Annual Meeting, Auckland, New Zealand

March 19-20, 2015: Interregional Association for Clinical Microbiology and Antimicrobial Chemotherapy (IACMAC) South Conference, Rostov-on-Don, Russia

March 24-26, 2015: The 2015 TB Summit, London, England

March 26-28, 2015: 6th Annual Consortium of Universities for Global Health (CUGH) Conference, Boston, MA

April 25-28, 2015: 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Copenhagen, Denmark

May 15-19, 2015: Congreso de la Asociacion Panamericana de Infectologia (API) Quito, Ecuador

May 20-22, 2015: International IACMAC Congress, Moscow, Russia

May 30-June 2, 2015: 115th General Meeting of the American Society for Microbiology (ASM), New Orleans, LA

June 2-3, 2015: A World Without Antibiotics, Uppsala Health Summit, Uppsala, Sweden

June 16-19, 2015: International Conference on Prevention and Infection Control (ICPIC) Geneva, Switzerland

June 27-29, 2015: Association for Professionals in Infection Control and Epidemiology (APIC) Annual Conference, Nashville, TN, USA

September 18-21, 2015: The American Society for Microbiology (ASM) and the International Society of Chemotherapy for Infection and Cancer (ISC) host ASM's Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the ISC's International Congress of Chemotherapy (ICC), San Diego, California, USA

October 15-16, 2015: IACMAC Volga Region Conference on Antimicrobial Therapy, Saratov, Russia

See more events

Antibiotic Resistance in the News

Pharma giant Merck buys Cubist, a victory for antibiotic development

On December 8th the internet was abuzz with the news that Merck, the pharmaceutical titan, had recently concluded a deal to acquire Cubist Pharmaceuticals, a company known for antibiotics research and development. This move is thought to signal the re-entrance of big pharma into the antibiotics field which has been in the spotlight as more and more antibiotics become obsolete in the face of growing resistance. With the rise of superbugs and warnings from the WHO and CDC about the imminent rise of health care costs associated with them, the stage has been set for companies to enter the pursuit of new classes of antibiotics.

WHO takes next step on Global Action Plan against antimicrobial resistance

On Dec 2-3, the WHO convened 30-35 Member States and other stakeholders in a Stockholm, Sweden, conference titled *Surveillance of Antimicrobial Resistance for Local and Global Action*. The meeting aimed to raise awareness and commitment towards developing and implementing a global surveillance program for antimicrobial resistance in human health. The expected outputs were to include: 1) an Outcome Statement indicating commitment to national action, 2) a Roadmap for the development of global AMR surveillance and 3) the Launch of International Collaboration to build global AMR surveillance, starting with a feasibility testing phase for the collection and sharing of data using the proposed surveillance standards. The Stockholm meeting follows the launch of a pivotal WHO report on antimicrobial resistance issued in April 2014 and will be followed by release of the current plan at the World Health Assembly in May and by further focus on antibiotic resistance at the Uppsala Health Summit on June 2-3, 2015.

CDC reports decline in vancomycin resistance genes

In a 7-year study of VRE (vancomycin resistant enterococcus and MRSA - methicillin-resistant Staph aureus) isolates from two Michigan health care institutions, CDC researchers have reported a decline in the genes responsible for vancomycin resistance. The prevalence of Inc 18, a gene that allows bacterial transfer among enterococci, was significantly lower in isolates tested after 2009 (1.5%) 2.5% of MRSA were positive for pSK41, supporting a decline in the gene's

prevalence. The trend is notable for its impact on preserving vancomycin as a last resort drug for treating MDR bacteria.

UK report issues startling predictions on antimicrobial resistance

In response to the UK Prime Minister's request for ideas to counter the growing threat of antimicrobial resistance, a commissioned team, chaired by Jim O'Neill, has issued its first paper outlining the problem: "Antimicrobial Resistance: tackling a crisis for the health and wealth of nations." The group makes the alarming projection that by 2050 antimicrobial resistant infections will kill 10 million globally – exceeding deaths caused by cancer—and associated costs will rise to $100 trillion. The group believes the crises can be averted, however, by taking the right steps quickly. In a sequential release of reports, the group will address the following:

- How changes in antimicrobial drug use can reduce antimicrobial resistance and how advances in genetics, genomics and computer science can facilitate it
- How the development of new antimicrobials can be supported
- How alternative therapies can be utilized to disrupt escalations in resistance
- The need for an international plan of action that coordinates regulation and drug use across sectors (humans, animals and environment).

A recommended package of actions for international agreement is anticipated by the summer of 2016.

PEW cites gaps in FDA's antibiotics policy

In Dec 2013, the U.S. Food and Drug Administration (FDA) released *Guidance #213* , which requested voluntary removal of growth-promotion uses on labels of antibiotics employed in food animals. In response, the PEW Charitable Trusts has issued a document citing gaps in the policy that need to be addressed. Of the 287 antibiotics reviewed by PEW, 66 had labels with overlapping growth promotion and disease-prevention dosages, with no limits on duration. All drugs are either critically important (29) or highly important (37) to human disease treatment. According to Gail Hansen of PEW, "FDA's policy is an important step, but there is more work to do, both to effectively eliminate growth promotion and to ensure that antibiotics are prescribed by veterinarians to prevent disease only under well-defined circumstances."

APUA®

"Preserving the Power of Antibiotics"®

About us

Antibiotics are humanity's key defense against disease-causing microbes. The growing prevalence of antibiotic resistance threatens a future where these drugs can no longer cure infections and killer epidemics run rampant. The Alliance for the Prudent Use of Antibiotics (APUA) has been the leading global non-governmental organization fighting to preserve the effectiveness of antimicrobial drugs since 1981. With affiliated chapters in more than 65 countries, including 33 in the developing world, we conduct research, education and advocacy programs to control antibiotic resistance and ensure access to effective antibiotics for current and future generations.

Our global network of infectious disease experts supports country-based activities to control and monitor antibiotic resistance tailored to local needs and customs. The APUA network facilitates the exchange of objective, up-to-date scientific and clinical information among scientists, health care providers, consumers and policy makers worldwide.

The APUA Newsletter has been published continuously three times per year since 1983.

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